UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,744	03/25/2005	Noboru Maki	053466-0395	7902

22428 7590 12/14/2007
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
12/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,744	MAKI ET AL.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/24/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *7-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/25/05;5/25/05;6/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction election

1. The Office acknowledges the receipt of Applicant's restriction election, filed on August 24, 2007. Applicant elects **with traverse** Group I, Claims 1-6 and 21 for examination.

2. The traversal is on the ground(s) that the cited Schlicht reference does not describe or teach the technical feature of Group I. The present invention is directed to a HBV precore protein, which is identified from HBe antigen-positive serum, contains all or part of a signal sequence, and forms a core particle (See specification, [0018] and [0019]). This means that a particle containing the pre-C sequence was formed from the HBV gene (Emphasis added by Applicant). However, Schlicht does not teach an HBV precore protein that forms particles. Moreover, the present specification describes that serum of a patient infected with HBV contains HBV particles formed from the HBV pre-core protein of the present invention, at a high frequency, and therefore, the present invention is clinically useful. Therefore, Schlicht does not describe or suggest the technical feature of Group I, and all Groups should be examined together.

3. Applicant's arguments are considered but found not persuasive for the following reasons: According to PCT Rule 13.1, an inventive concept considered as a whole is assessed to determine if a special technical feature exists over the prior art. Here, Claim 1 recites: "A HBV precore protein that has an ability of forming the core-like particles of HBV and that contains all or part of the signal sequence" (Emphasis added). The inventive concept of HBV precore protein of Group I is taught by Schlicht.

4. First, Schlicht teaches a recombinant vaccinia construct e-VAC, which encodes a full-

length precore protein (see Figure 1B, and line 1-3, right col., p.6819. Also see cited reference #28, Schlicht 1989). The HBV precore protein produced by e-VAC appears to have the *N*-terminus of the amino acid sequence at position -28 and the *C*-terminus is at positions 150-154 (see Figures 1B and 2, pp. 6818 and 6819). Schlicht also teaches the recombinant precore protein, such as p22e shown in Figure 3, appears to have same physical property as the claimed HBV precore protein p22.

5. Secondly, Schlicht's precore protein "has an ability of forming the core-like particles of HBV" (Claim 1), as evidenced by Schlicht 1998 (See Materials and Methods, Para 1, right col. p. 5399), and Junker reference cited as reference #15 in Schlicht 1989. Junker teaches that plasmid pMH3/3091, which is the parent construct of e-VAC, contains precore initiation codon (Para 2, p. 10121), and is able to form Dane particles (core like particles) (See Para 1, p. 10125). Thus, Schlicht's precore protein "has an ability of forming the core-like particles of HBV". In view of the entirety of Schlicht, Schlicht's HBV precore protein appears to have same structural features, physical and biological properties as the HBV precore protein described in the claims of Group I.

6. Finally, although Schlicht teaches a recombinant HBV precore protein, while the claimed HBV precore protein is from serum samples, the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) See MPEP 2113. Moreover, Schlicht's recombinant HBV precore protein could also be clinical useful.

7. Therefore, the inventive concept of HBV precore protein of Group I is taught by the prior art in view of the entirety of Schlicht reference. The requirement is still deemed proper and is therefore made FINAL.

8. Accordingly, Claims 1-21 are pending. Claims 7-20 are withdrawn as non-elected. Claims 1-6 and 21 are considered in this Office action.

Information Disclosure Statement

9. The information disclosure statements submitted on March 25, and May 25, 2005, and June 21, 2006, are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner. The initialed and dated copies of Applicant's IDS form 1449 are attached to the instant Office action.

Foreign Priority

10. Receipt is acknowledged of certified copy of foreign priority papers JP2002-261666 submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objection

11. Claim 4 is objected to because of the following informalities: The terms "HBV core (like) particles" and "HBV virus (like) particles" should be "HBV core-like particles" and "HBV virus-like particles" for clarity.

Claim Rejections - 35 USC § 101 Utility

12. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions

and requirements of this title.

13. Claims 1-4 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. "A HBV precore protein" or "HBV core like particles comprising the HBV precore protein" of Claim 1-4 is a product of nature. Products of nature do not constitute patentable subject matter under 35 U.S.C. § 101. Amending the claims to "an isolated HBV precore protein" and/or "a purified HBV precore protein" and "isolated HBV core-like particles" would overcome this rejection.

Claim Rejections - 35 USC § 112, second paragraph

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1 and 3-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

16. Claim 1 is indefinite because it is not clear to what the phrase "the signal sequence" refers. Different signal sequences are described in the specification, for example "signal peptide of 19 residues at the N-terminal thereof" in Para [0005], two transcriptional initiation signals precore gene in Para [0007] and [00018], "the signal sequence or the HBe sequence portion (amino acid Nos. -10 to 149)" in Para [0019], etc. HBV precore protein is a precursor protein, which can be processed into more than one protein, like procore protein, e antigen and core antigen. Thus, it contains more than one signal sequence. It is not clear to what specific signal

sequence for what specific function "the signal sequence" of Claim 1 refers. This rejection affects all dependent claims.

Claim Rejections - 35 USC § 112, first paragraph

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 1 and 4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detail chemical structure of the encompassed genus of undefined nucleotide fragment, proteins or polypeptides. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Lid.*, 18 USPQ2d 1016.

19. Claim 1 is directed to an HBV precore protein that has an ability of forming the core-like particles of HBV and that contains all or part of the signal sequence. Claim 4 is directed to HBV

core like particles or HBV virus like particles comprising the HBV precore protein according to Claim 1.

20. Claims 1 and 4 lack written description because the essential feature of the claimed "HBV virus like particles comprising the HBC precore protein" (Claim 4) and "the signal sequence" of HBV precore protein (Claim 1) that is responsible for forming "HBV virus like particles" of Claim 4 are not described by the specification, and are not conventional in the art or known to one skilled in the art.

21. The prior art teaches that a precore protein is an intermediate viral product, which is a precursor of the core protein and e antigen (Schlicht, 1991, cited in IDS, see p. 6817). The prior art does not teach that the HBV precore protein is incorporated into HBV particles (Nassal, 1997, cited in IDS. See Figure 1A). Although the applicant discloses that the precore protein can self-form a particle in the specification, the specification has not shown any HBV-like particles that contain a precore protein, or a precore particle is assembled into HBV-like particle. The specification has not disclosed the structural features of such HBV-like particles, nor "the signal sequence" of HBV precore protein (Claim 1) that is responsible for forming "HBV virus like particles". Thus, the claimed "HBV like particle comprising precore protein" is not described by the specification, and is not conventional in the art or known to one skilled in the art.

22. Consequently, while the skilled artisan would reasonably conclude Applicant was in possession of an HBV core protein, there is no indication that Applicant was in possession of HBV virus-like particles comprising the HBC precore protein.

Claim Rejections - 35 USC § 112, first paragraph-Scope of Enablement

23. Claims 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a HBV core-like particle comprising a precore protein, does not reasonably provide enablement for a HBV-like particle comprising a precore protein, and does not reasonably provide enablement for HBV precore protein as a therapeutic agent or a vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech Inc. v. Novo Nordisk 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); In re Wright 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); In re Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in In re Wands 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

24. Claim 4 reads on a HBV-like particle comprising a HBV precore protein that has an ability of forming the core-like particles of HBV and that contains all or part of the signal sequence. The claim lacks enablement requirement because the claimed HBV-like particle comprising the HBV procore protein is not adequately described by the specification as

discussed above (See Para 21). One of ordinary skill in the art would not know how to make it from the disclosure.

25. Claim 5 is directed to a HBV vaccine or a therapeutic agent comprising the HBV precore protein. Claim 5 does not meet the enablement requirement because the instant specification does not teach how to use the claimed HBV precore protein as a therapeutic agent or a vaccine.

26. It is known in the art that the HBV surface protein HBsAg has been used as HBV vaccine (Chang, 2006, J. Clin Virol. 36 Suppl. 1 S45-S50. entire document). The prior part art also teaches that HBV core protein, HBc, can be used as vaccine carrier moiety (Schodel, 1996). However, the prior art did not teach use of HBV precore protein as a therapeutic agent or a vaccine. Therefore, it is not predictable how HBV precore protein would work as an alleged therapeutic agent or alleged vaccine

27. The instant specification has not previded any teaching regarding the clinical application of HBV precore protein. The specification has characterized that HBV precore protein in sera can self-form a particle, but fails to teach specifically how to use this HBV precore protein as a vaccine or a therapeutic agent. The specification does not disclose what diseases the claimed HBV precore protein can be used to against or treat. There is no any specific data in the specification showing that the HBV precore protein would be effective as a vaccine for preventing HBV infection. As a result, one of ordinary skill in the art can not use the instant invention without such teaching.

Claim Rejections - 35 USC § 102

28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

29. Claims 1, 2, 4-6 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Takahashi (J. Immunology, 147(9): 3156-3160, 1991, cited in IDS).

30. Claims 1, 4-6 and 21 are directed to a HBV precore protein, or an HBV core-like particle, that has an ability of forming the core-like particles of HBV and that contains all or part of the signal sequence, and an HBV diagnostic reagent or a diagnostic kit comprising the HBV precore protein. Claim 2 is directed to a HBV precore protein that has an ability of forming the core-like particles of HBV, in which the *N*-terminus of the amino acid sequence is at position -28 and the *C*-terminus is at positions 150-154.

31. Takahashi teaches that an HBV procore protein from sara samples pooled from 70 subjects infected by **HBV subtype adr strain.** Takahashi teaches that the HBV precore protein has an ability to form Dane particle (a core-like particle) such as $p20^e$ (see abstract and Para 5, p. 3157, p.31; Results, p.3157-3159, Figure 3). Takahashi teaches that $p20^e$ contains the signal peptide MQLFHLXLII at its *N*-terminus. Takahashi also teaches that $p20^e$ does not react with mAB2212 that binds to the carboxyl-terminus of HBc $p21^c$, suggesting that $p20^e$ does not contain amino acids 150-154 of the carboxyl-terminus of HBc $p21^c$. Theses teachings anticipates Claims 1, 2 and 4-6. Takahashi also teach detecting, isolating and diagnosing precore proteins. This teaching anticipates Claim 21. Therefore, the instant claims are anticipated by Takahashi.

Claim Rejections - 35 USC § 103

32. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

33. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi (J. Immunology, 147(9):3156-3160, 1991, cited in IDS), in view of Kobayash.

34. The relevance of Takahashi is set forth *supra.*

35. Takahashi does not explicitly teach the HBV precore protein has SEQ ID NO: 1.

36. Kobayashi teaches the HBV precore protein of adr strain, which is 99.6% identical to the instant SEQ ID NO: 1, as evidenced by sequence alignment. Kobayashi teaches that the HBV precore protein of adr strain differ from the claimed HBV precore protein SEQ ID NO:1 only by coding protein having amino acid V, rather than T, at position 119 of the precore protein.

37. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an HBV precore protein that has SEQ ID NO: 1, because one of ordinary skill in the art would recognize that the instant SEQ ID NO: 1 is an obvious variant of the precore protein of HBV adr strain taught by Takahashi and Kobayashi. It would be predictable that the SEQ ID NO: 1 would have the ability to form a core-like particle, given that SEQ ID NO: 1 is highly identical to the precore of HBV adr strain, and amino acid change V119T appears to locate in protein coding region, not in a signal sequence, as taught by Kobayashi, and also given that the HBV precore of adr strain is able to form an precore particle,

as shown by Takahashi.

"[W]hen one steps back and views the twisted structure of the protein as a whole, and considers the overall similarity of the protein of the prior art versus that coded for by the DNA claimed herein, and also considers the similarity of the DNA of the prior art versus that claimed herein, the minor change in the chemical configuration or design of the molecule discovered or made by appellants is so negligible that a *prima facie* case of obviousness exists. In legal parlance, on the record herein appellants' structural modification is *de minimis*." Ex parte Anderson, 30 USPQ2d 1866

38. Thus, in view of the structural and functional equivalence of the claimed precore protein SEQ ID NO: 1 with the HBV precore protein taught in the prior art, use of precore protein SEQ ID NO: 1 is a design choice. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Remarks

39. No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph.D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Bo Peng, Ph.D.
November 20, 2007

MARY E. MOSHER, PH.D.
PRIMARY EXAMINER